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# Gut/brain Axis and its Role in Parkinson's Disease Progression

by Kendra Myers

## Abstract

The gut/brain axis has a significant role in disease progression in Parkinson's disease. There are several hypotheses for what is causing the progression itself; one of which is that the microbiome in the GI is creating SCFAs that are able to increase inflammation,  $\alpha$ -synuclein originates in the GI and is able to travel to the brain causing  $\alpha$ -synuclein aggregation and inflammation, and that the overall inflammation in the brain is causing activation of microglia causing increased  $\alpha$ -synuclein aggregation. It is unknown which of these is causing the disease, but they all have been shown to have a role. It is known that  $\alpha$ -synuclein aggregates cause motor symptoms and there is evidence to show that it originates from the dysbiosis of the GI microbiota.  $\alpha$ -synuclein in the CNS activates microglia cells, increasing proinflammatory cytokines TNF- $\alpha$  and IL-6. The short chain fatty acids produced by fermentation byproducts of the gut microbiome play a role on the enteric nervous system and can be a major player of the nonmotor symptoms displayed by Parkinson's disease patients and increasing inflammation. Lastly, the microbiome of Parkinson's disease patients is altered from a normal gut microbiome to a disease-causing form. All of these factors play a role in Parkinson's disease progression but the main treatment (L-DOPA) does not directly impact any of these factors.

## Introduction

Parkinson's disease is the second leading neurological disease in adults over the age of 65 (Ganjavi et al., 2015). It is a multifactorial disease that is strongly influenced by environmental factors (Nalls et al., 2014). The pathological features of Parkinson's are caused when dopaminergic neurons in the substantia nigra significantly restrict the supply of dopamine to the dorsal aspect of the striatum (Varanese et al., 2010; Liddle, 2018; Ganjavi et al. 2015). The reduction in functioning dopaminergic neurons is caused by the

formation of Lewy bodies that are made by the presence of  $\alpha$ -synuclein (Liddle, 2018). Alpha-synuclein is a 140 amino acid protein that can form an incorrect structure and move from cell to cell, in a prion like fashion (Liddle, 2018), causing other dopaminergic neurons to have this misfolded protein and lead to further loss of dopamine (Liddle, 2018).

The loss of dopamine causes significant motor dysfunction (Varanese et al., 2010; Ganjavi et al., 2015). Motor symptoms can be greatly improved with

the standard treatment of Levodopa (Ganjavi et al., 2015; Varanese et al., 2010). The motor symptoms are treatable but only to an extent. Nonmotor symptoms of Parkinson's are increasingly recognized cause of significant disability (Varanese et al., 2010; Ganjavi et al., 2015). These symptoms consist of dementia, psychosis, depression, anxiety, sleep disorders, dysphagia, and constipation (Varanese et al., 2010; Ganjavi et al., 2015).

#### Current Parkinson's Treatment

The discovery of Levodopa, L-3,4-dihydroxyphenylalanine, (L-DOPA) by Arvid Carlsson (Carlsson et al., 1957), has been the treatment of choice for therapeutic management of Parkinson's disease. To this day L-DOPA is the most commonly used treatment due to its efficacy for relief in symptoms. Even though it is good at treating the symptoms there are still some major problems with the drug after the clinical benefit has been reached (Ganjavi et al., 2015). Some of these limitations are postural abnormalities, autonomic dysfunction, cognitive dysfunction, anxiety and drug-related side effects, such as L-DOPA-induced dyskinesia (LID) (Varanese et al., 2010; Ganjavi et al., 2015). LID occurs because of the dosage fluctuating between high and low due to oral dosing (Varanese et al., 2015).

L-DOPA is usually given orally several times per day due to its relatively short half-life in plasma (Nutt, 2008). L-DOPA is also usually given with carbidopa, to prevent its conversion to dopamine in the peripheral nervous system allowing it to get to the central nervous system where L-DOPA is able to cross the blood brain barrier (Stansley and Yamamoto, 2015). Even though the increase in dopamine in the brain shows some improvement with symptoms, preclinical and clinical evidence suggests that L-DOPA treatment might be causing a worsening affect (Eskow Jaunarajs et al., 2012). The dopamine that is produced by L-DOPA is mediated in part by serotonin neurons and the increase of dopamine causes an oxidative stress that is damaging to serotonin neurons (Stansley and Yamamoto, 2015). L-DOPA is able to help with the symptoms of Parkinson's but does not stop disease progression.

#### Central nervous system

The central nervous system is a very large network of neurons that is the command center for the entire body. The vagus nerve connects the enteric nervous system to the central nervous system. Since the vagus nerve goes from the brain to the abdominal area, regulates abdominal organ function. 20% of the fibers are responsible for communication from the brain to the

ENS whereas the other 80% are for communication from the ENS to the brain (Figure 1, Breit et al., 2018). It is thought that  $\alpha$ -synuclein travels through the vagus nerve to get to the brain (Pamontujo et al., 2010).

Enteric nervous system

The GI tract consists of the enteric nervous system (ENS) made up of the myenteric and the submucosal plexi, these neurons are responsible for the smooth muscle relaxation and contraction and can be influenced by sympathetic and parasympathetic stimuli from the brain. The enteric

nervous system and glial cells form a vast communication network that is in close proximity to the gut microbiome thus the enteric nervous system can be influenced by the bacteria in the gut (Caputi and Giron, 2018). This also means that the ENS can be affected by microbiome alterations. It is speculated that this could also be a cause of GI disorders and neurodegenerative disease. Therefore, the ENS can be a potential entry point for pathogens as well as therapeutic interventions based on diet and/or commensal microbiomes-derived molecules (Endres and Schäfer, 2018).

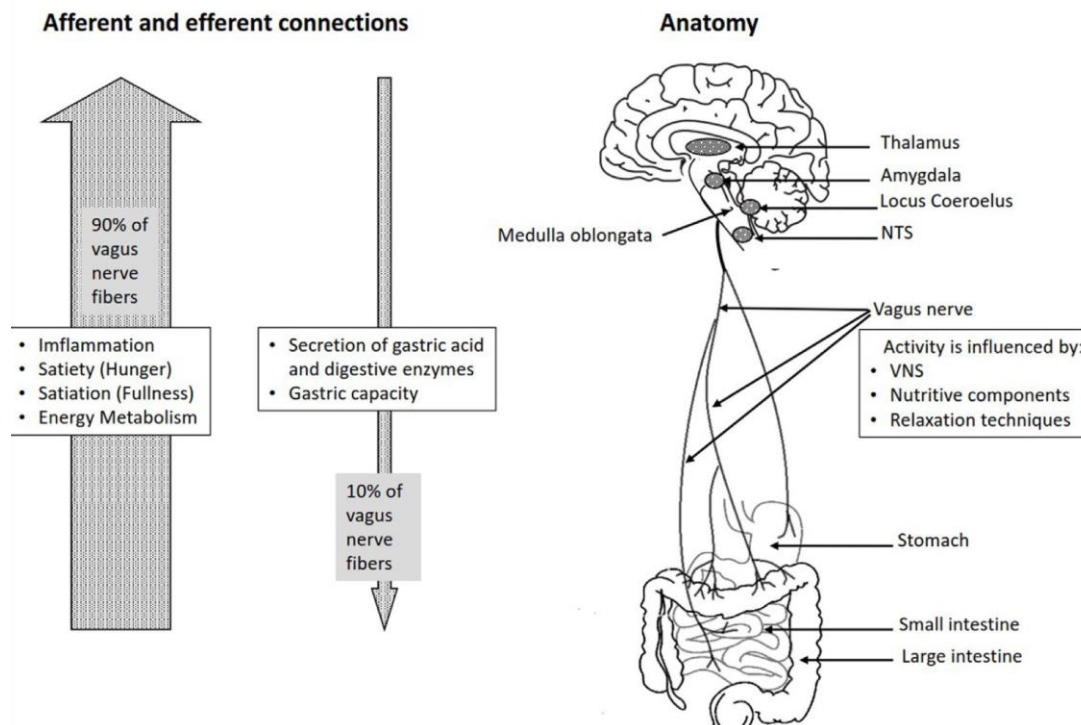


Figure 1. Basic anatomy and function of the gut/brain access (Breit et al., 2018). This shows that the vaugs nerve originates in the brain and projects to the GI system. In the vagus nerve 20% of the nerve fibers are used for communication from the brain to the GI system whereas the other 80% of these nerves are used for communication from the GI system to the brain.

### Gut/brain access and the microbiome

The gut/brain access is defined as the bidirectional communication between the central nervous system, autonomic nervous system, and enteric nervous system (CNS, ANS, ENS respectively) through the vagus nerve (Figure 1, Breit et al., 2018; Mayer et al., 2015; Caputi and Giron, 2018). The role of both commensal and pathogenic organisms, has been recognized to influence the gut-brain access (Grenham et al., 2011). The bacteria in the GI tract are able to influence the neurons in the GI tract as they can synthesize neurotransmitters and neuromodulators, for example serotonin, dopamine, and short-chain fatty acids (Mulak et al., 2015; Mayer et al., 2015). This cellular communication between the bacteria in the gut and neurons in the ENS, has led to speculation that this communication can be a drug delivery system to get a neurotransmitter to the CNS.

### **Discussion**

#### Dysbiosis of microbiome

Parkinson's disease patients have an altered microbiome (Hasegawa et al., 2015; Keshavarzian et al., 2015; Scheperjans et al., 2015). When samples of human gut microbiomes were taken and given to germ free (GF) mice, there was a direct correlation

between the disease status of the human donor and disease outcome in the GF mice recipients (Figure 2, Sampson et al., 2018). The humanized mouse groups that received transplants from PD donors had very similar microbial communities when compared to each other, whereas the humanized mouse groups that received transplants from healthy donors had more diversity (Sampson et al., 2018).

There was also an altered number of genera between PD transplanted animals compared to animals with transplants from healthy donors (Sampson et al., 2018). The change in microbial diversity in PD patients was found to have an increase in genetic diversity of *Proteus sp.*, *Bilophila sp.*, and *Roseburia sp.*, but there was a loss of members in Lachnospiraceae, Rikenellaceae, and Peptostreptococcaceae families as well as *Butyricoccus sp.* (Sampson et al., 2018). Furthermore animals with PD donor transplants had significantly altered short chain fatty acid profile with a lower concentration of acetate, and higher relative abundances of propionate and butyrate, when compared to animals that received transplants from healthy donors (Sampson et al., 2018).

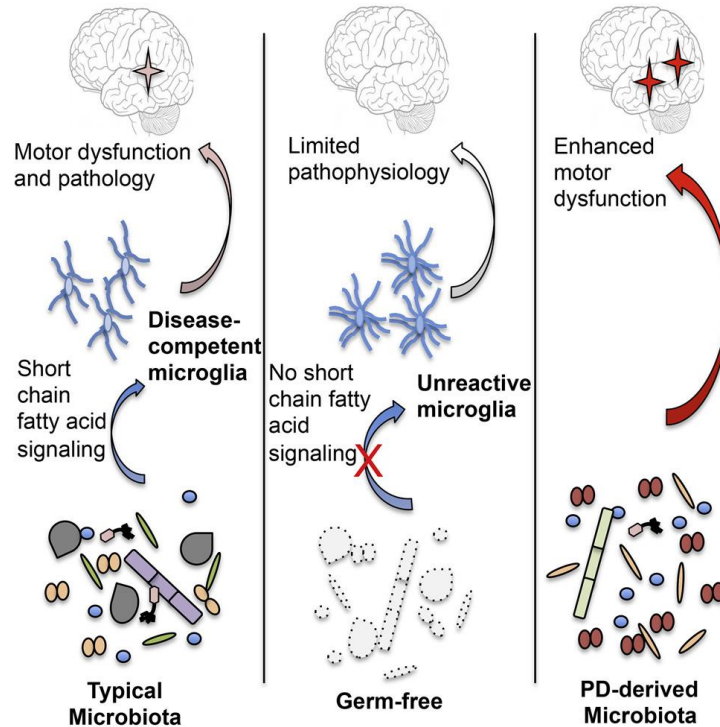


Figure 2. The left column shows how the microbiome of the gastrointestinal tract influences disease progression when a typical microbiome is established. The middle column shows when no microbiota is established, and the animal is germ free. The last column shows when Parkinson's disease derived microbiota is established causing major motor dysfunction. (Sampson et.al, 2018)

What is causing dysbiosis of the microbiome in Parkinson's disease patients? Evidence suggests that specific pesticide exposure is able to impact the microbiome configuration causing a microbial imbalance (Ascherio and Schwarzschild, 2016). There is also speculation that  $\alpha$ -synuclein may act as an antimicrobial and is able to shape the microbiome (Sampson et al., 2018). Whatever the cause may be, the Parkinson's microbiota is either missing or has reduced protective microbes, and/or has pathogenic bacteria causing the disease. The dysbiosis will cause a differential production of microbial

molecules in the GI and metabolites produced by this unbalanced microbiome may enter blood circulation and reach the brain, impacting neural function.

### Short Chain Fatty Acids

Gut bacteria are able to modulate microglia activation through production of microbial metabolites known as short chain fatty acids (Erny et al., 2015). These short chain fatty acids include acetic acid, propionic acid, and butyric acid (Smith et al. 2013). Short chain fatty acids are able to cross the blood brain barrier and impact physiology of

the cells in the CNS or they can impact nerves in the periphery, indirectly activating mature microglia by unknown mechanisms (Mitchell et al., 2011; Erny et al., 2015). They have been shown to cause worsening effects in animals that already show motor dysfunction (Sampson et al., 2018). In the same study, germ free –  $\alpha$ -synuclein overexpressing mice (GF – ASO) that were treated with heat-killed bacteria and were fed with short chain fatty acids, also showed motor deficits (Sampson et al., 2018). However when short chain fatty acids along with an anti-inflammatory compound (minocycline) are fed to GF – ASO, they showed reduced TNF-  $\alpha$  production, reduced  $\alpha$ -synuclein aggregates, and improved motor function (Sampson et al., 2018).

Both Sampson et al. and Unger et. al., showed that there is a reduction of short chain fatty acids in fecal samples from mice (Sampson et al., 2018) and human (Unger et al., 2016) Parkinson's disease microbiome. There was a significant reduction of acetate, propionate, and butyrate in the fecal samples. Butyrate interacts with the local colonic mucosa and ENS neurons, increasing colonic activity (Soret et al., 2010; Kidd and Schneider, 2010). Reversely, when butyrate concentrations are low it is associated with dysmotility causing

constipation in patients (Yamada et al., 2014).

### $\alpha$ -synuclein Pathology

The unregulated expression of  $\alpha$ -synuclein in humans leads to an increased risk of Parkinson's disease (Soldner et al., 2016). In Parkinson's disease, motor deficits coincide with  $\alpha$ -synuclein aggregation and Lewy body formation (Liddle, 2018; Sampson et al., 2018). This occurs due to  $\alpha$ -synuclein aggregation in specific parts of the brain. The  $\alpha$ -synuclein aggregation is observed in caudoputamen and substantia nigra, found in the nigrostriatal pathway in the brain (Brettschneider et al., 2015; Sampson et al., 2018). In Sampson et al. they compared alpha synuclein overexpressing (ASO) animals to the GF-ASO animals, they found that GF-ASO animals displayed less  $\alpha$ -synuclein aggregates (Sampson et al., 2018). They also found that there was a regional specificity for  $\alpha$ -synuclein aggregation (Sampson et al., 2018). There was more  $\alpha$ -synuclein aggregation in the specific pathogen free (SPF) animals than the GF-ASO animals in the frontal cortex but in the cerebellum there was no difference (Sampson et al., 2018). Therefore, the microbiota could regulate the different pathways that promote  $\alpha$ -synuclein aggregation, prevent the clearance of

insoluble protein aggregates or accomplish both simultaneously.

Microglia activation

The microbiota is able to regulate immune development in the CNS and  $\alpha$ -synuclein aggregates to activate immune cells, including brain-resident microglia (Matcovitch-Natan et al., 2016; Kim et al., 2013; Sanchez-Guajardo et al., 2013; Erny et al., 2015). When the microglia are activated they undergo major morphological changes, the cell bodies transition from numerous branched extensions to round, amoeboid cells with fewer branches (Figure 3, Lecours et al. 2018; Erny et al., 2015). This change in the microglia

leads to increases pro-inflammatory cytokine tumor necrosis factor -  $\alpha$  (TNF- $\alpha$ ) and interleukin-6 (IL-6) (Sampson et al., 2018). Both cytokines are increased in the brains of Parkinson's disease patients (Mogi, Harada, Riederer, et al., 1994; Mogi, Harada, Kondo, et al., 1994). The neuroinflammatory responses are region specific with increased microglia diameter and TNF- $\alpha$  production in the frontal cortex but not the cerebellum (Sampson et al., 2018). This supports that the gut microbes can promote  $\alpha$ -synuclein aggregates within specific brain regions involved in disease.

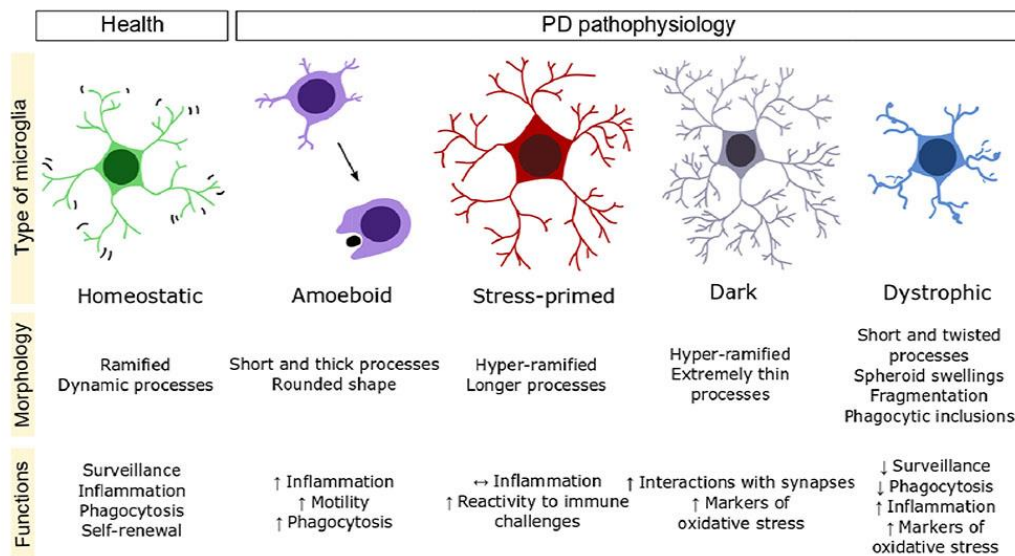


Figure 3. Microglial alterations found in Parkinson's disease pathophysiology. In healthy individuals the microglia function properly and have good projections. In Parkinson's patients there are four other possible microglial morphologies. The amoeboid morphology has short thick processes and causes increased inflammation, motility and phagocytosis. Stress-Primed is very sensitive to immune challenges. Dark has increased interactions with synapses and have extremely thin projections. Lastly, the Dystrophic has short twisted processes and has decreased surveillance and phagocytosis but increased inflammation. (Lecours et. al, 2018)



## Conclusion

Even though Parkinson's disease is classified as a neurodegenerative disease, the gut microbiome has many roles in the disease progression. This paper shows that there is evidence to support dysbiosis of the gut microbiome allows production of  $\alpha$ -synuclein aggregates in the brain. The dysbiosis also alters the concentrations of short chain fatty acid synthesis in the gut, which can lead to increased production of pro inflammatory cytokines. Inflammation has a role in the activation of microglia, which increases

inflammation in the brain causing more activation in the brain and more damage (Figure 4). Since it was demonstrated, when the microbiome from a Parkinson's disease patient is given to an animal then that animal develops motor deficits. Led to the thought that a probiotic specific for Parkinson's disease that would be able to alter the gut microbiome back to a non-diseased state would be a potential area of research and treatment option. Another area of future research could be to look at the use of anti-inflammatory drugs in reducing inflammation and motor deficit.

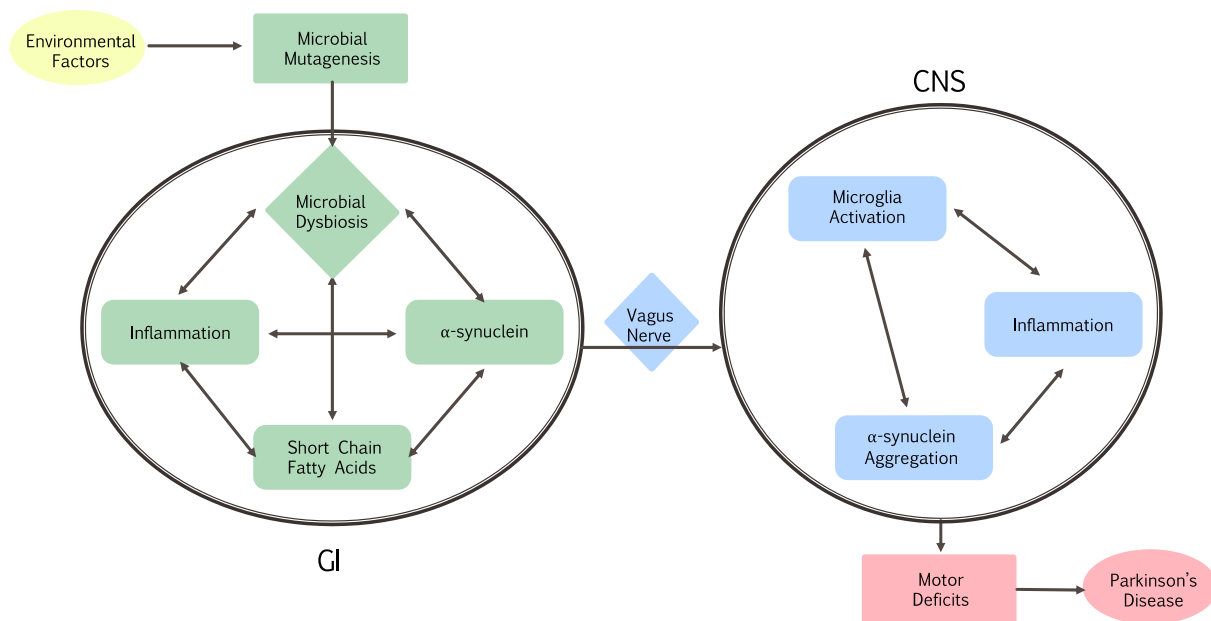


Figure 4. Parkinson's disease pathogenesis. Environmental factors affect microbial community causing dysbiosis. The dysbiosis in the GI tract then has an effect on alpha-synuclein, short chain fatty acid synthesis and inflammation, with all of these factors compounding each other. It is thought that alpha-synuclein and some of the short chain fatty acids are able to migrate via the vagus nerve to the brain. When they arrive in the brain, alpha-synuclein and short chain fatty acids cause neuro inflammation activating microglia. The microglia become more active increasing inflammation and alpha-synuclein aggregation, causing Parkinson's disease.

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